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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/827,493 | 04/06/2001 | Lenard M. Lichtenberger | 96606/15UTL | 5746 |

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| EXAMINER | |
|---|---|
| JIANG, SHAOJIA A | |
| **ART UNIT** | **PAPER NUMBER** |
| 1617 | |

DATE MAILED: 02/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/827,493 | LICHTENBERGER, LENARD M. | |
| | Examiner | Art Unit | |
| | Shaojia A Jiang | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *33-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32 and 46-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This Office Action is a response to Applicant's amendment and response to the Office Action (mailed May 7, 2003), filed October 7, 2003 wherein claims 46-48 are newly submitted.

Currently, claims 1-48 are pending in this application.

Claims 33-45 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention (see the previous Office Actions May 7, 2003).

Claims 1-32 and 46-48 are examined on the merits herein.

Applicant's second declaration of Dr. Lenard M. Lichtenberger (inventor) submitted October 7, 2003 under 37 CFR 1.132, is acknowledged and will be further discussed below.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-32 and 46-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over DAIFOTIS, et al. (WO 9904773, of record) in view of Lichtenberger et al. (5,763,422, of record), further in view of Hovancik et al.

(5,869,471, of record) for the reasons of record in the previous Office Action May 7, 2003.

Daifotis et al. discloses that bisphosphonates such as alendronate, risedronate, tiludronate and ibandronate, within the instant claims, are known to be useful in pharmaceutical compositions and methods for treating osteoporosis. See abstract, page 1 lines 14-15 and page 2 lines 1-15. Daifotis et al. also discloses that bisphosphonates are known to have low bioavailability from GI tract and therefore cause adverse GI effects. See abstract, page 1-3. Further, Daifotis et al. discloses that the purpose of the methods therein are for inhibiting bone resorption in mammals to treat osteoporosis while minimizing the adverse GI effects (see abstract and page 7 lines 22-23 in particular). Daifotis et al. also discloses the effective amounts of bisphosphonates to be administered in the compositions therein for minimizing the adverse GI effects (see Examples at page 24-27)

Daifotis et al. do not expressly disclose the employment of one zwitterionic phospholipid to reduce GI toxicity of bisphosphonate when administering at least one bisphosphonate in a pharmaceutical composition. The prior art does also not expressly disclose the effective amounts of active agents in the composition herein to be administered.

Lichtenberger et al. disclose that the particular zwitterionic phospholipids, within the instant claims, (see abstract, col.3 lines 59-67, col.10 lines 50-62, col.11 lines 60-65) are capable of reducing GI irritating (adverse) effects and is therefore useful broadly in combining with many NSAID drugs (see Table I at

col.4 lines 25-52) in pharmaceutical compositions since NSAID drugs may cause GI adverse effects, e.g., inducing GI ulcers and bleeding. See also abstract and col.1-2. Lichtenberger et al. also disclose the effective amounts of zwitterionic phospholipids in the pharmaceutical compositions therein. See col.12 lines 12-34.

Hovancik et al. discloses that the combination of NSAIDs and bisphosphonates is useful in improving the therapeutic effect for treating arthritis (bone disorders) (see col. 1-3, especially col.3 lines 3-7).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine one zwitterionic phospholipid to reduce GI toxicity of bisphosphonate when administering at least one bisphosphonate in a pharmaceutical composition, and to optimize the effective amounts of active agents in the composition herein to be administered.

One having ordinary skill in the art at the time the invention was made would have been motivated to combine one zwitterionic phospholipid to reduce GI toxicity of bisphosphonate when administering at least one bisphosphonate in a pharmaceutical composition since zwitterionic phospholipids are known to be capable of reducing GI irritating (adverse) effects that caused by other drugs such as many NSAIDs according to Lichtenberger et al. Moreover, bisphosphonates such as alendronate, risedronate, tiludronate and ibandronate are known to cause adverse GI effects and the purpose of the method of Daifotis et al. is known to minimize the adverse GI effects induced by bisphosphonates. Further, the combination of NSAIDs and bisphosphonates is known to be useful

in methods for treating bone disorders, and the combination of NSAIDs and zwitterionic phospholipids is also known to be useful in methods for treating bone disorders.

Therefore, one of ordinary skill in the art would have reasonably expected that combining one zwitterionic phospholipid and a bisphosphonate in a composition to be administered would reduce or minimize adverse GI effects induced by the bisphosphonate. Hence, the combined teachings of Daifotis and Lichtenberger Hovancik have provided the motivation of the instant invention.

Additionally, one of ordinary skill in the art would have been motivated to optimize the effective amounts or ratio of zwitterionic phospholipid and a bisphosphonate in a composition because the effective amounts of zwitterionic phospholipid to be administered are known in the art. Moreover, the optimization of amounts of active agents to be administered is considered well within the skill of artisan, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Applicant's remarks and the second declaration of Dr. Lenard M. Lichtenberger (inventor) submitted October 7, 2003 under 37 CFR 1.132 with respect to this rejection of claims 1-32 made under 35 U.S.C. 103(a), of record stated in the Office Action dated May 7, 2003 have been fully considered but are

not deemed persuasive as to the nonobviousness of the claimed invention over the prior art for as further discussed below.

Again, Applicant arguments that there is no motivation to combine because there is no reasonable expectation that their combination would be successful are not found persuasive. As Applicant admits, Daifotis et al. clearly teaches that bisphosphonates can cause adverse GI effects when ingested. Daifotis et al. also disclose that their invention relates to methods for inhibiting bone resorption in mammals to treat osteoporosis while minimizing the occurrence of or potential for adverse GI effects (see page 1 lines 11-13). Thus, the teachings of Daifotis et al. are seen to provide the motivation to make the present invention in reducing GI toxicity induced by bisphosphonates.

Moreover, zwitterionic phospholipids (within the instant claims) are known to be capable of reducing GI irritating (adverse) effects and are therefore useful broadly in combining with NSAID drugs in pharmaceutical compositions in order to reduce GI adverse effects, e.g., inducing GI ulcers and bleeding, caused by NSAID drugs, according to Lichtenberger et al. As discussed in the previous Office Action, one of ordinary skill in the art, therefore, would have reasonably expected that combining one zwitterionic phospholipid and a bisphosphonate in a composition to be administered would reduce or minimize adverse GI effects induced by the bisphosphonate with reasonable expectation for success, absent evidence to the contrary.

Additionally, Hovancik et al. has been cited by the examiner primarily for its teachings of that the combination of NSAIDs and bisphosphonates is useful in

improving the therapeutic effect for treating arthritis (bone disorders) (see col. 1-3, especially col.3 lines 3-7), further supports the examiner's position, since that the combination of NSAIDs and bisphosphonates is known to be useful in methods for treating bone disorders, and the combination of NSAIDs and zwitterionic phospholipids is also known to be useful in methods for treating bone disorders. Thus, one of ordinary skill in the art would reasonably expect that the combination of bisphosphonates and zwitterionic phospholipids would be successful in treating bone disorders, the same disorders, absent evidence to the contrary.

Applicant's arguments regarding that "the motivation to combine these to references is derived exclusively from hindsight" have been considered but are not found persuasive. It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin, 170 USPQ 209 (CCPA 1971). See MPEP 2145.

Therefore, as discussed above, motivation to combine the teachings of the prior art to make the present invention is seen and no improper hindsight is seen. The claimed invention is clearly obvious in view of the prior art.

Dr. Lichtenberger's second declaration herein is ineffective to overcome the 103(a) rejection herein since it is not seen to provide clear and convincing evidence of nonobviousness or unexpected results. The declaration merely

presents the testing result for the single particular bisphosphonate, risedronate, in combination with the single particular zwitterionic phospholipid, DPPC, and/or also combing indomethacin (a NSAID), to be administered orally to rats. However, the evidence in the declaration is not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the bisphosphonates (a genus) and zwitterionic phospholipids (a genus) in the claimed composition. See MPEP § 716.02(d).

Further, Applicant asserts that "This data shows just how unpredictable combinations of even well known pharmaceuticals can be". Nonetheless, the data in diagrams, figures, and tables herein are unclear as to how the graphical, diagram and table presentations herein may be taken to demonstrate unexpected effect in the instant invention. Moreover, the clear explanation of pointing out exactly what facts are established therein and relied upon by applicant is not seen in the declarartion. Applicant has the burden to explain the experimental evidence. See *In re Borkowski and Van Venrooy* 184 USPQ 29 (CCPA 1974).

Therefore, the declaration is insufficient to rebut the prima facie case herein.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

In view of the rejections to the pending claims set forth above, no claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9307. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
February 20, 2004

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER
10/22/04